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(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL–6824 BM Arnhem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LEYSEN, Dirk [BE/BE]; Kerkstraat 26, B–3920 Lommel (BE). KELDER, Jan [NL/NL]; Beethovengaarde 97, NL–5344 CD Oss (NL).

(74) Agent: KRAAK, H.; P.O. Box 20, NL–5340 BH Oss (NL).

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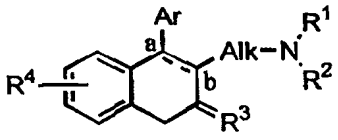
(54) Title: NOVEL ARYL–HYDRO NAPHTHALENAL KANAMINES

(57) Abstract

The invention describes an aryl–hydronaphthalenalkanamine, having structural formula (I). The invention also provides a pharmaceutical composition comprising such a compound and the use of such a compound to effectuate partial or complete blockade of serotonergic 5–HT_{2C} receptors in an organism. Furthermore the inventio provides a process for the preparation of such a compound.



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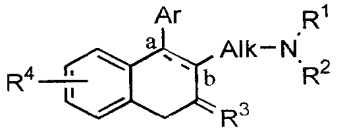
Novel Aryl-hydronaphthalenalkanamines

This invention relates to novel aryl-hydronaphthalenalkanamines, to a process for the preparation thereof and to the use of these compounds for the preparation of compositions for the blockade of serotonergic receptors in living organisms.

Aryl-hydronaphthalenalkanamines and the preparation thereof are described in Morrison and Rinderknecht (1950). A 1-phenyl-3,4-dihydro-*N,N*-dimethyl-2-naphthalenemethanamine and a 1-phenyl-1,2,3,4-tetrahydro-*N,N*-dimethyl-2-naphthalenemethanamine were prepared in view of a putative structural relationship to morphine and were expected to have an analgesic effect. However, these compounds did not have the analgesic effect aimed for and have not found their way to any other use.

The present invention provides aryl-hydronaphthalenalkanamines, which unexpectedly have biological activity due the blockade of serotonergic 5-HT_{2C}-receptors. The compounds of this invention are aryl-hydronaphthalenalkanamines having the structural formula (I),



Formula (I)

wherein

R^1 and R^2 each independently are H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, C_4-C_6-cycloalkenyl or C_1-C_6-alkoxy-C_1-C_6-alkyl; preferred is that R^1 is methyl and R^2 is a hydrogen or a methyl;

R^3 is (H,H) or (H,CH_3);

R^4 is hydrogen or one or more substituents at the 5, 6, 7 or 8 position of the naphthyl group;

Ar is a phenyl, naphthyl or heteroaryl group, each of which optionally having one or more substituents;

Alk is C_2-C_6-alkylene, C_3-C_6-alkenylene or C_3-C_6-alkynylene, each of which has 2 - 3 carbon atoms between the naphthalene-ring and the amine function, and can be branched, unbranched or cyclised;

the dotted line between a-b is an optional double bond; the cis position is preferred;

or addition salts and solvates thereof.

A compound of this invention can have chiral centres at the carbon atoms labelled as a and b. For these locations the racemic mixtures as well as the enantiomers are made available by this invention.

The terms as used here have the following meaning:

A substituent is a group selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfonyl, C_2-C_6 alkenyloxy, C_2-C_6-alkenylthio, C_2-C_6-alkenylsulfonyl, C_2-C_6-alkynyloxy, C_2-C_6-alkynylthio, C_2-C_6-alkynylsulfonyl, aminocarbonyl, cyano , halo, trihalomethyl, aminosulfonyl, nitro and di(C_1-C_6)-alkylamino.

C_1-C_6-alkyl is a branched, unbranched or cyclised saturated hydrocarbon with 1 - 6 carbon atoms.

C_2-C_6 alkenyl is a branched, unbranched or cyclised unsaturated hydrocarbon with 2 - 6 carbon atoms and at least one double bond.

C_2-C_6-alkynyl is a branched, unbranched or cyclised unsaturated hydrocarbon with 2 - 6 carbon atoms and at least one triple bond.

A heteroaryl group means a C_2-C_{14}-aromatic group including one or two aromatic rings containing one or more (for example, one to three) heteroatoms selected from oxygen, sulfur, and nitrogen. Examples of such groups are thienyl, furanyl, benzofuranyl, 1,2-benzoisoxazolinyl, pyridinyl, thiadiazolinyl, indazolinyl, benzofuranyl, quinolinyl, and isoquinolinyl.

Halo- or halogen means F, Cl, Br or I.

Preferred embodiments of this invention are compounds wherein

R^1 is methyl and R^2 is a hydrogen or a methyl;

R^3 is H,H;

R^4 is hydrogen;

Ar is phenyl with halo- or trihalomethyl-substituents;

Alk is ethylene.

When there are stereoisomers at a single 1,2 bond in the naphthalene group the cis position is preferred.

Most preferred compounds of this invention are (±)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine and (±)-*cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine and the (+)-enantiomers of these compounds.

The compounds of the present invention possess biological activity due to the partial or complete blockade of the serotonin 5-HT_{2C} receptor. Such a property can be used in medical and veterinary practice. While it is possible for a compound of the present invention to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention also makes available a pharmaceutical composition comprising a compound according to formula I in admixture with a pharmaceutically acceptible carrier. A carrier must be "acceptable" in the sense of being compatible with the other ingredients of the composition while not being deleterious to the recipients thereof. Furthermore, a compound according to formula I can be used for the manufacture of a composition to effectuate partial or complete blockade of serotonergic 5-HT_{2C} receptors in an organism.

Serotonin has the function of a hormone or a neurotransmitter in most living organisms. Serotonin acts in the organism by interacting with its receptors. The serotonin receptor changes its conformation when serotonin binds to it. This conformational change induces in turn changes in the biochemical processes in an organism. Compounds which bind to serotonin receptors, without inducing the serotonin induced conformational change, will prevent access of serotonin to the receptor and thus prevent its natural action. Such blockade of serotonin receptors changes the physiology of an organism.

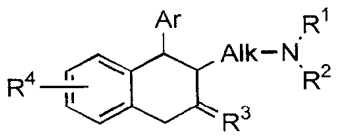
There are 14 different types of receptors for serotonin. Of these, the 5-HT_{2C} receptor is important for functions of the central nervous system. Since it was shown that

serotonin in the brain of mammals mediates fear and other emotional reactions, the compounds of this invention can be used in medicines for treating anxiety and other diseases of the mind and the central nervous system.

This can be demonstrated with in vitro and in vivo methods and reveals itself in therapeutic usefulness of compounds of this invention. In particular, these compounds can be used for the preparation of a medicament for the treatment of psychiatric and neurological diseases, such as anxiety disorders, affective disorders, psychotic disorders, adjustment disorders, somatisation disorder, central pain disorder, migraine, anorexia nervosa and in the prophylaxis of diseases such as migraine and epilepsy. In particular the treatment of generalised anxiety is expected to be improved by the use of compounds of this invention as medicines. To treat these conditions, the compounds can be administered on a regular basis, in suitable amounts, to a mammal, such as a human, believed to be suffering from the particular condition.

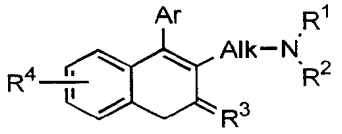
The compounds in this invention with the highest selectivity for the 5-HT_{2C} receptor, in particular when there is a much smaller affinity for the 5-HT_{2A} receptor, are preferred compounds in view of a reduced chance for side effects. Such compounds are in particular the most preferred compounds (±)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine and (±)-*cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine and their (+)-enantiomers, which can be used as medicines in relatively low doses in view of their high potency. With such properties the chance for side effects is even further reduced.

The compounds of this invention can be made by various routes of synthesis.



Formula (II)

According to a first general process A, compounds of formula (II), wherein R^1, R^2, R^3, R^4, Alk and Ar are as hereinbefore defined, may be prepared by dihydro-addition of compounds of formula (III).



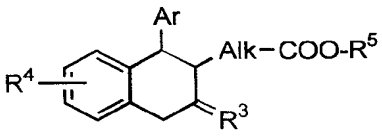
Formula (III)

This reduction may be carried out using methods well known in the art or readily available from the chemical literature. Such methods include the reaction with hydrogen in the presence of a suitable hydrogenation catalyst, either heterogeneous or homogeneous; transfer hydrogenation using transition-metal catalysts or by using non-catalytical reagents such as zinc and acids, hydrazine and hydrides in the presence of transition metal salts. The reduction is typically carried out by catalytical hydrogenation, using a heterogeneous catalyst, such as platinum, rhodium, ruthenium and preferably palladium on charcoal, in the presence of a polar solvent such as methanol or ethanol, at temperatures of 0°C to 60°C and a hydrogen pressure between 1 and 5 atm.

For the enantioselective hydrogenation of the prochiral compounds (III), optically active homogeneous, as well as heterogeneous catalysts may be used. For example, using methods and catalysts described in Advanced Organic Chemistry, J. March, 4th Ed, pages 772-773, 1992.

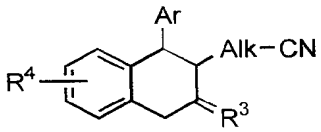
Compounds of formula (II) wherein R^1 and R^2 are different from -H, can also be obtained by reaction of compounds of formula (II) wherein R^1 and/or R^2 are hydrogen, with an appropriate alkylating agent. Suitable alkylating agents include halides and organic and inorganic esters. The reaction may be carried out in the presence of a base in a polar solvent such as an alcohol or *N,N*-dimethylformamide at an elevated temperature.

Alternatively, these compounds can be prepared by reductive alkylation, for example the Leuchart-Wallach reaction, using carbonyl compounds such as ketones or aldehydes and formic acid or formamides or the Eschweiler-Clarke reaction.



Formula (IV)

According to a second general process B, compounds of formula (II), especially when R^1 and/or R^2 are -H, may also be prepared by reduction of an appropriate amide, prepared from compounds of formula (IV), wherein R^5 is a C_1-C_6-alkyl group, by for example ester hydrolysis, formation of an acyl halide or anhydride and reaction with a suitable amine. Compounds of formula (IV) are well known from the literature, for example C.L. Hewett, J. Chem. Soc., 596 (1936) and M.S. Newman and L.M. Joshel, J. Am. Chem. Soc., **62**, 972 (1940). For the reduction of the amide group, catalytic hydrogenation eventually at high temperatures and pressures, sodium borohydride in the presence of certain catalysts, borane, sodium in propanol, trichlorosilane and preferentially chlooralanes or lithium aluminium hydride in a non-protic solvent such as diethyl ether or tetrahydrofuran at elevated temperatures can be used.



Formula (V)

Alternatively, compounds of formula (II), wherein R^1 and R^2 are both -H, can be prepared from compounds of formula (V) by reduction of the nitrile group into a primary amine by well known standard conditions such as lithium aluminium hydride, borane-methyl sulfide complex, catalytical hydrogenation or sodium borohydride in the presence of cobalt(II) chloride or Raney nickel.

Compounds of formula (V) are well described in the chemical literature, for example T. Yamashita *et al*, J. Org. Chem., **61**, 6438 (1996).

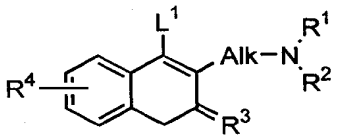
If the nitriles of formula (V) are converted into nitrilium salt by treatment with trialkyloxonium salts, reduction may produce compounds of formula (II), wherein R^1 or R^2 are different from -H.

Alternatively, compounds of formula (II) may be synthesised from compounds of formula (V) by reduction of the nitrile into an aldehyde, for example using tin(II) chloride and hydrochloric acid or a metal hydride reducing agent followed by hydrolysis, and subsequent transformation of the aldehyde group into an amine by reductive alkylation using ammonia, a primary or secondary amine in the presence of, for example, hydrogen and a hydrogenation catalyst.

Formula (VI)

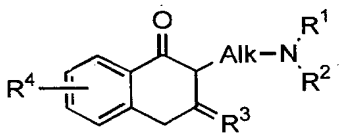
According to a third general process C, compounds of formula (II) may be prepared by dehydroxylation of compounds of formula (VI) by catalytic hydrogenolysis, for example using Raney nickel as a catalyst, or reduction using hydrides such as lithium aluminium hydride, sodium borohydride or triethylsilane in the presence of Lewis acids. Alcohols of formula (VI) can also be reduced indirectly by conversion of the -OH function into a leaving group such as a sulfonate or an halide and subsequent reduction using lithium aluminium hydride, sodium borohydride or diisobutylaluminium hydride.

Alternatively, compounds of formula (III) may be synthesised by dehydration of alcohols of formula (VI) using acids such as sulfuric acid or phosphoric acid, metallic oxides or other well known dehydrating agents.



Formula (VII)

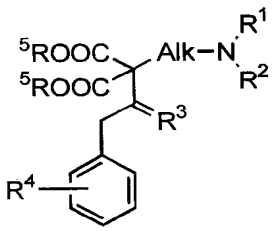
According to a fourth general process D, compounds of formula (III), wherein R^1 and R^2 are both different from hydrogen, may be obtained by a cross-coupling reaction of compounds of formula (VII), wherein L^1 is an appropriate leaving group, preferentially a halide or triflate group, with an optionally substituted aryl- or heteroaryl-lithium, -magnesium, -zinc and preferably -boron reagent using well known palladium salts or complexes, bases and polar solvents, as described in Palladium Reagents and Catalysts, J. Tsuji, pages 209-227, 1995.



Formula (VIII)

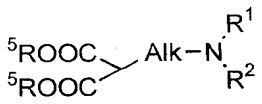
Compounds of formula (VII) may be prepared by the conversion of compounds of formula (VIII) into vinyl halides using inorganic acid halides, preferentially by treatment with phosphorus pentachloride, or into vinyl triflates, for example, by treatment with a strong base such as lithium hexamethyldisilazane and a triflating reagent such as *N*-phenyltrifluoromethanesulfonamide in an apolar solvent at temperatures ranging from -70°C to 60°C.

According to a fifth general process E, compounds of formula (VI) may be obtained by addition of an organometallic reagent such as a Grignard or aryllithium reagent, derived using methods well known to a person skilled in the art from a compound Ar-L^2, wherein Ar is as hereinbefore described and L^2 is a suitable leaving group such as a nitro-, mesylate- or triflate- group or a halide, including fluoro, chloro, bromo or iodo, to a compound of formula (VIII).

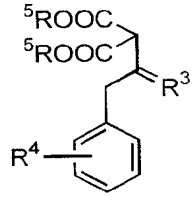


Formula (IX)

According to a sixth general process F, compounds of formula (VIII) may be prepared from compounds of formula (IX), wherein R^5 is a C_1-C_6-alkyl, by ester hydrolysis, subsequent decarboxylation and aromatic acylation. Ester hydrolysis can be catalysed by acids or bases. The decarboxylation can be effectuated by well known methods such as heating the free acid or its salt, eventually in the presence of catalysts, for example various inorganic salts or a suitable crown ether. For the final cyclisation, a Friedel-Crafts acylation may be applied. The free carboxylic acid as well as acyl halides, anhydrides and ketenes can be used for this acylation, as well as catalysts such as Lewis acids or proton acids, when the reagent is a carboxylic acid. Preferentially, compounds of formula (VIII) can be obtained from compounds of formula (IX) by treatment with an inorganic base such as sodium or potassium hydroxide in a polar solvent such as a mixture of alcohols with water and heated at elevated temperature. After acidification with an inorganic acid, the intermediate dicarboxylic acid is decarboxylated by heating at elevated temperatures, for instance ranging from 100°C to 300°C, and cyclised by reacting the residue with a proton acid, preferentially concentrated sulfuric acid at elevated temperatures, for example ranging from 20°C to 100°C.



Formula (X)



Formula (XI)

According to a seventh general process G, compounds of formula (IX) may be prepared from compounds of formula (X), or alternatively from compounds of formula (XI), by alkylation with an appropriate reagent, containing a suitable leaving group such as a nitro-, mesylate- or triflate- group or a halide, including fluoro, chloro, bromo or iodo. For this alkylation a base may be used, preferentially a strong base as for example sodium hydride, in a polar non-protic solvent such as dimethyl sulfoxide or N,N-dimethylformamide at temperatures ranging from 0°C to 150°C. Alternatively crown ethers or phase transfer conditions can be employed.

The individual enantiomers of compounds of formula (II) may be prepared as hereinbefore described or obtained from a mixture of stereoisomers using any method well known in the art for separating such isomers into their constituent enantiomers. For example, using methods described in Stereochemistry of organic Compounds, E.L. Eliel and S.H. Wilen, chapter 7, 1994. In particular they may be obtained by conversion to diastereomers by methods such as salt formation with optically active acids followed by fractional crystallisation or by differential absorption using columns packed with chiral material, for example by preparative chiral liquid or gas chromatography.

For the preparation of a pharmaceutical composition comprising a compound of formula I a compound of this invention can be mixed with one or more suitable carriers. Some examples of suitable carriers are various carbohydrates, gum acacia, calcium phosphate, gelatin, talc, magnesium stearate or mineral oil.

Suitable pharmaceutical compositions include those adapted for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. A dosage unit may contain between 0.005 mg and 2000 mg of a compound of the present invention. Usually, for treatment of anxiety administration of 1 to 4 dosage units of the pharmaceutical composition of the invention per day is sufficient for obtaining a therapeutic effect. The therapy may be continued for as long as necessary or desired.

The compositions may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro *et al.*, Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical Preparations and their manufacture). Such methods include the process of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients, carrying out said process by exclusion of contamination with traces of pathogens and harmful chemicals. Accessory ingredients include those conventional in the art, such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents and wetting agents.

Compositions adapted for oral administration may be presented as discrete units such as tablets or capsules each containing a predetermined amount of active ingredient; as powder or granulates; as a solution or suspension. The active ingredient may also be presented as a bolus or paste, or may be contained within liposomes or microparticles.

Compositions adapted for rectal administration may be presented as a suppository or enema.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection fluids. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Compositions adapted for sublingual administration may be presented as liquid, solids or lozenges, which can comprise a rapidly disintegrating composition of a pharmaceutically acceptable water-soluble or water-dispersible carrier material. Such carrier materials are well known in the art and can be polysaccharides like hydrolysed dextran, dextrin, mannitol, and alginates, or mixtures thereof, or mixtures thereof with other carrier materials like polyvinylalcohol, polyvinylpyrrolidone and water-soluble cellulose derivatives, like hydroxypropyl cellulose.

Compositions adapted for nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurised aerosols, nebulisers or insufflators.

Compositions may, for example, be presented in a suitable sustained release form, for example, in a device such as the Minipump™.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

Example 1 : [2-(dimethylamino)ethyl](2-phenylethyl)-propanedioic acid diethyl ester

A total of 16 grams of a 60% dispersion of sodium hydride in mineral oil was washed with heptane. Thereafter 150 ml of *N*,*N*-dimethylformamide were added and a solution of 49 grams of (2-phenylethyl)-propanedioic acid diethyl ester in 350 ml of *N*,*N*-dimethylformamide was added dropwise. The resulting reaction mixture was stirred at 60°C during 2 hours. After cooling at room temperature, 30 grams of 2-dimethylaminoethylchloride hydrochloride were added portionwise. After stirring at 60°C for 16 hours, the resulting mixture was poured into water and extracted with diethyl ether. The organic layers were collected and washed with 1N aqueous hydrochloric acid. The aqueous layers were collected, the pH was adjusted at pH 10-11 with aqueous sodium hydroxide and extracted several times with diethyl ether. After drying over sodium sulfate, and evaporating the solvent under reduced pressure, 46.8 grams of crude [2-(dimethylamino)ethyl](2-phenylethyl)-propanedioic acid diethyl ester were obtained, with a GC purity of 82%.

In a similar way was prepared :

- [3-(dimethylamino)propyl](2-phenylethyl)-propanedioic acid diethyl ester,
- [2-(dimethylamino)ethyl](3-phenyl-2-propyl)-propanedioic acid diethyl ester.

Example 2 : 2-[2-(Dimethylamino)ethyl]-3,4-dihydro-1(2*H*)-naphthalenone

A total of 46.8 grams of crude [2-(dimethylamino)ethyl](2-phenylethyl)-propanedioic acid diethyl ester were dissolved into a solution of 33.5 grams of potassium hydroxide in 180 ml of water and 90 ml of ethanol. The reaction mixture was heated at 100°C during 3 hours, cooled to 0°C and treated with 50 ml of concentrated hydrochloric acid. The resulting mixture was evaporated to dryness under reduced pressure. The residue was heated at 160°C during 4 hours. The solid obtained was added slowly to 175 ml of concentrated sulfuric acid. After stirring at 60°C for 2 hours, this mixture was neutralised with aqueous sodium hydroxide and extracted twice with ethyl acetate. The organic layers were collected, dried over sodium sulfate and evaporated to dryness under reduced pressure to afford 18.25 g of 2-[2-(dimethylamino)ethyl]-3,4-dihydro-1(2*H*)-naphthalenone, GC purity : 99%,
M.S. (C.I.) (M/Z) : 217 $[M]^+$.

In a similar way were prepared :

- 2-[3-(dimethylamino)propyl]-3,4-dihydro-1(2*H*)-naphthalenone, M.S. (C.I.) (M/Z) : 231 $[M]^+$,
- 2-[2-(dimethylamino)ethyl]-3,4-dihydro-3-methyl-1(2*H*)-naphthalenone, M.S. (C.I.) (M/Z) : 231 $[M]^+$,
- 2-[2,2-dimethyl-2-(dimethylamino)ethyl]-3,4-dihydro-1(2*H*)-naphthalenone, M.S. (C.I.) (M/Z) : 245 $[M]^+$.

Example 3 : 2-[2-(Dimethylamino)ethyl]-1,2,3,4-tetrahydro-1-phenyl-1-naphthalenol ethanedioate (1:1)

To a solution of 1.95 g of : 2-[2-(dimethylamino)ethyl]-3,4-dihydro-1(2*H*)-naphthalenone in 20 ml of dry diethylether, previously cooled at 0°C, were added under an atmosphere of nitrogen, 11 ml of a 2M solution of phenyllitium in cyclohexane/diethyl ether (7/3). The resulting mixture was allowed to reach room temperature. After stirring for another 16 hours, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated to dryness under reduced pressure to yield 3.4

grams of a crude product which was purified by chromatography on silica gel, eluting with toluene/ethanol (95/5) to afford 1.5 grams 2-[2-(dimethylamino)ethyl]-1,2,3,4-tetrahydro-1-phenyl-1-naphthalenol. A total of 0.2 grams of this compound was dissolved in ethanol and a solution of 0.067 grams of ethanedioic acid in ethanol was added. After precipitation and recrystallisation from ethanol/diethyl ether, 0.094 grams of 2-[2-(dimethylamino)ethyl]-1,2,3,4-tetrahydro-1-phenyl-1-naphthalenol ethanedioate (1:1), m.p. : 137°C.

Example 4 : 3,4-Dihydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine hydrochloride

A suspension of 1.35 grams of 2-[2-(dimethylamino)ethyl]-1,2,3,4-tetrahydro-1-phenyl-1-naphthalenol in 75 ml of a 2N aqueous solution of hydrochloric acid was stirred at 100°C during 30 minutes. After cooling at 0°C, the precipitate was filtered off to yield a compound which after recrystallisation from ethanol/diethyl ether afforded 1.0 gram of 3,4-dihydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine hydrochloride, m.p. : 209°C.

Example 5 : Trifluoromethanesulfonic acid 2-[2-(dimethylamino)ethyl]-3,4-dihydro-1-naphthalenyl ester

Under an atmosphere of nitrogen, 112 ml of a 1N solution of lithium hexamethyldisilazane in tetrahydrofuran were added to a solution of 15.8 grams of 2-[2-(dimethylamino)ethyl]-3,4-dihydro-1(2*H*)-naphthalenone in 365 ml of dry tetrahydrofuran, previously cooled at -70°C. After stirring at -70°C for 1 hour, 39.6 grams of *N*-phenyltrifluoromethanesulfonamide were added in one portion. The resulting mixture was allowed to reach room temperature and stirred for 16 hours. Thereafter, water was added to the mixture, which was extracted with ethyl acetate. The organic layer was washed successively with a saturated solution of ammonium chloride in water and a saturated aqueous solution of sodium chloride, dried over sodium sulfate and evaporated to dryness under reduced pressure to yield 54 grams

of crude product, containing 47% of trifluoromethanesulfonic acid 2-[2-(dimethylamino)ethyl]-3,4-dihydro-1-naphtalenyl ester (GC-purity).

In a similar way was obtained :

- crude trifluoromethanesulfonic acid 2-[3-(dimethylamino)propyl]-3,4-dihydro-1-naphthalenyl ester,
- crude trifluoromethanesulfonic acid 2-[2-(dimethylamino)ethyl]-3,4-dihydro-3-methyl-1-naphtalenyl ester,
- crude trifluoromethanesulfonic acid 2-[2,2-dimethyl-2-(dimethylamino)ethyl]-3,4-dihydro-1-naphthalenyl ester,

Example 6 : 1-(4-Fluorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1)

A total of 33 grams of the crude product obtained under example 5 was dissolved in 225 ml of ethyleneglycol dimethylether and 95 ml of a 2M aqueous solution of sodium carbonate. To this mixture were added 3.7 g of tetrakis(triphenylphosphine)palladium(0), 8.1 grams of lithium chloride and 12.45 grams of 4-fluorobenzeneboronic acid. The resulting suspension was heated at reflux for 16 hours and cooled at room temperature. After the addition of water, the mixture was extracted with diethyl ether. The organic layers were collected and extracted with a 2N aqueous solution of hydrochloric acid. After collection, the pH of the aqueous layers was adjusted with sodium hydroxide to pH 10-11, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure to yield 12.2 grams of 1-(4-fluorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine (95% pure on GC). This residue was dissolved in ethanol and an excess of ethanedioic acid was added. After precipitation with diethyl ether, the resulting solid was recrystallised from ethanol/diethyl ether to afford 11 grams of 1-(4-fluorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 196°C.

In a similar way were prepared :

- 3,4-dihydro-*N*,*N*-dimethyl-1-(2-methylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 171°C,
- 1-(3-aminophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 158°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(3-nitrophenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 163°C
- 3,4-dihydro-*N*,*N*-dimethyl-1-(4-trifluoromethylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 170°C,
- 3,4-dihydro-1-(3-methoxyphenyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 180.5°C,
- 3,4-dihydro-1-(4-methoxyphenyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 170°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(4-methylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 187°C,
- 1-(4-chlorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethaneamine ethanedioate (1:1), m.p. : 193°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(4-trifluoromethylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 179°C,
- 1-[4-(dimethylamino)phenyl]-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 204.5°C,
- 1-[4-(1,1-dimethylethyl)phenyl]-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 197°C,
- 1-(2,4-dichlorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 165°C,
- 1-(3,5-dichlorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 203°C,
- 1-(3-chloro-4-fluorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethaneamine ethanedioate (1:1), m.p. : 194°C,
- 3,4-dihydro-1-(2-thienyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 166°C,

- 3,4-dihydro-1-(3-thienyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 195.5°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(3-pyridinyl)-2-naphtaleneethanamine ethanedioate (1:2), m.p. : 154.3°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(4-pyridinyl)-2-naphtaleneethanamine ethanedioate (1:2), m.p. : 234°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(1-naphthalenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 120°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-(2-naphthalenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 198°C,
- 1-(2-benzofuranyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 162°C,
- 3,4-dihydro-*N*,*N*-dimethyl-1-phenyl-2-naphthalenepropanamine (Z)-2-butenedioate (1:1), m.p. : 111°C,
- 1-(4-fluorophenyl)-3,4-dihydro-*N*,*N*-dimethyl-2-naphthalenepropanamine (Z)-2-butenedioate (1:1), m.p. : 117°C,
- 3,4-dihydro-*N*,*N*,α,α-tetramethyl-1-phenyl-2-naphthaleneethaneamine ethanedioate (1:1), m.p. : 145°C,
- 3,4-dihydro-*N*,*N*,3-trimethyl-1-phenyl-2-naphthaleneethanamine ethanedioate (1:1), M.S. (C.I.) (M/Z) : 291 $[M]^+$

Example 7 : *cis*-1,2,3,4-Tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine hydrochloride

To a suspension of 4.7 grams of 3,4-dihydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine ethanedioate (1:1) in 100 ml of ethanol, was added 1.1 gram of 10% palladium on activated charcoal. This suspension was hydrogenated in a Parr apparatus using 2 atm of hydrogen pressure during 70 hours. The resulting mixture was filtered and the filtrate evaporated to dryness under reduced pressure, yielding 4.1 grams of a solid. This residue was recrystallised from ethanol/diethyl ether, yielding 3.8 grams of *cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine ethanedioate (1:1), which was converted into the

hydrochloride salt by extraction of an alkaline aqueous suspension with diethyl ether, drying, evaporating to dryness and addition of 1.1 equivalents of hydrochloric acid, dissolved in dry ethanol. Recrystallisation from ethanol/diethyl ether afforded pure *cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine hydrochloride, m.p. : 206°C.

In a similar way were prepared :

- *cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-(2-methylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 166°C,
- *cis*-1-(3-aminophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 148°C,
- *cis*-1,2,3,4-tetrahydro-1-(3-methoxyphenyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 151°C,
- *cis*-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), M.S. (C.I.) (M/Z) : 309 $[M]^+$,
- *cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-(4-methylphenyl)-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 198°C,
- *cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 190°C,
- *cis*-1-[4-(dimethylamino)phenyl]-1,2,3,4-tetrahydro-N,N-dimethyl-2-naphthaleneethanamine athanedioate (1:1), M.S. (C.I.) (M/Z) : 322 $[M]^+$,
- *cis*-1-[4-(1,1-dimethylethyl)phenyl]-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 197°C,
- *cis*-1-(2-benzofuranyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine ethanedioate (1:1), m.p. : 130°C,
- *cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-napthalenepropanamine ethanedioate (1:1), m.p. : 118°C,
- *cis*-1,2,3,4-tetrahydro-*N*,*N*,α,α-tetramethyl-1-phenyl-2-naphthaleneethanamine ethanedioate (1:1), M.S. (C.I.) (M/Z) : 307 $[M]^+$.

Example 8 : (-)-*cis*-1,2,3,4-Tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1) and (+)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-

dimethyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1) by chiral HPLC separation

A total of 2.7 grams of *cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine hydrochloride, obtained from 3.8 grams of the ethanedioate (1:1) salt; described in example 7, was separated by chiral HPLC using a Chiracel OJ 500x20 mm column (Daicel Chem. Ind.) and eluting with hexane/ethanol : 95/5, containing 0.1% diethylamine at a flow of 10 ml/min at room temperature. The first fractions were combined and evaporated to dryness under reduced pressure to yield 1.09 grams of a solid, which was dissolved in ethanol and treated with 0.45 grams of (Z)-2-butenedioic acid. Recrystallisation from ethyl acetate/diethyl ether affords 1.35 grams of (-)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 127.9°C.
In a similar way, from the second fraction, 0.9 grams were obtained of (+)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 128°C.

In a similar way were prepared :

- (+)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-(4-methylphenyl)-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 150°C,
- (-)-*cis*-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-1-(4-methylphenyl)-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 150°C,
- (+)-*cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 148°C,
- (-)-*cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 145°C,
- (+)-*cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), M.S. (C.I.) (M/Z) : 265 $[M]^+$,
- (-)-*cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), M.S. (C.I.) (M/Z) : 265 $[M]^+$.

Example 9 : (+)-*cis*-1-(4-Fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1) by fractional crystallisation using chiral acids

A total of 2.8 grams of *cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine, obtained from 3.7 grams of the ethanedioate (1:1) salt; described in example 5, was dissolved in ethanol and 3.8 grams of (-)-di-1,4-toluyl-L-tartaric acid were added. The precipitate was recrystallised several times from ethanol until the solid was pure on chiral HPLC. This solid was converted into the free base, dissolved in ethanol and 1.1 equivalents of (Z)-2-butenedioic acid were added. Recrystallisation from ethanol/diethyl ether afforded 0.42 grams of (+)-*cis*-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-2-naphthaleneethanamine (Z)-2-butenedioate (1:1), m.p. : 148°C.

Example 10 : *cis*-1-phenyl-1,2,3,4-tetrahydronaphthyl-2-acetamide

To a suspension of 5.32 grams of *cis*-1-phenyl-1,2,3,4-tetrahydronaphthyl-2-acetic acid in 50 ml of dry dichloromethane were added 2.5 grams of thionyl chloride. The reaction mixture was stirred at room temperature for 48 hours. The resulting mixture was evaporated to dryness under reduced pressure and co-evaporated with toluene several times, to yield 3.8 grams of the crude acid chloride. This residue was taken up in 50 ml of dry dichloromethane and added to a large excess of methylamine. After stirring at room temperature for 4 hours, the resulting mixture was washed several times with water. The organic layer was collected, dried and evaporated to dryness under reduced pressure to afford 3.7 grams of *cis*-1-phenyl-1,2,3,4-tetrahydronaphthyl-2-acetamide, m.p. : 190°C.

Example 11 : *cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthaleneethanamine hydrochloride

A solution of 2.8 grams of *cis*-1-phenyl-1,2,3,4-tetrahydronaphthyl-2-acetamide in 25 ml of dry tetrahydrofuran was added to 40 ml of a 1.0 M solution of lithium aluminium hydride in tetrahydrofuran. The resulting mixture was heated at reflux for 2 hours. After cooling at room temperature, 8.0 ml of a saturated aqueous solution of sodium sulphate were added and the mixture was stirred for 15 minutes. Thereafter, 300 ml of diethylether, 80 grams of sodium sulphate and 22 ml of methanol were added and the resulting mixture was stirred at room temperature for 30 minutes. The precipitates were filtered off over hyflo and the resulting filtrate was evaporated to dryness under reduced pressure to afford 2.1 grams of crude *cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthalenenethaneamine. This residue was taken up in methanol and an excess of hydrocloric acid dissolved in methanol was added. After precipitation with diethyl ether and recrystallisation from methanol/diethyl ether 2.0 grams were obtained of *cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthaleneethanamine hydrochloride, m.p. : 182.5°C.

In a similar way were prepared :

- *cis*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthalenemethanamine hydrochloride, m.p. : 245°C,
- *trans*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthalenemethanamine hydrochloride, m.p. : 217°C,
- *trans*-1,2,3,4-tetrahydro-*N*-methyl-1-phenyl-2-naphthaleneethaneamine hydrochloride m.p. : 198°C.

Example 12: 5-HT_{2C} receptor binding assay

NIH/3T3 cells are stably transfected with cloned human 5-HT_{2C} receptors. Mesulergine binds reversibly to these receptors. Using labelled mesulergine the binding can be assessed by separation of bound and non-bound mesulergine. Specific binding of labelled mesulergine can be inhibited by 5-HT agonists (e.g.

serotonin) and 5-HT antagonists. In this example binding activity of compounds of this invention to cloned human $5HT_{2C}$ receptors is demonstrated by measuring the inhibition of mesulergine binding to these receptors.

Method

The following solutions are prepared:

A buffer solution containing Tris(hydroxymethyl)aminomethane (Tris), $MgCl_2$ and pargyline.

The buffer is prepared by dissolving Tris (6,06 g; 0,05 mol), ethylenediaminetetraacetic acid (EDTA; 0,19 g; 0,5 mmol), $MgCl_2.6H_2O$ (2,033 g; 10 mmol), ascorbic acid (1,0 g) and pargyline HCl (1,96 mg; 0,01 mmol) in approx 990 ml water. This solution is adjusted to pH 7,4 with HCl (4 $mol \cdot l^{-1}$) and made up to 1 l with water. The buffer is freshly prepared before use.

A solution containing labelled mesulergine solution:

A solution of L-[N-6-methyl-^{3}H] Mesulergine (specific activity approx 70 $Ci \cdot mmol^{-1}$) in ethanol (1,00 $mCi \cdot ml^{-1}$; TRK-845; Amersham Int., England) is stored under protection from light in sealed polypropylene tubes at -20 °C. Immediately before use 0,005 ml of this solution is made up to 2,94 ml with Tris-$MgCl_2$ buffer containing pargyline. An aliquot of 0,050 ml of this solution is used for each assay (final concentration $2 \cdot 10^{-9}$ $mol \cdot l^{-1}$ reaction mixture).

Tris-buffer:

Tris(hydroxymethyl)aminomethane (0,6 g; 0,005 mol) is dissolved in approx 950 ml water. This solution is adjusted to pH 7,4 with HCl (4 $mol \cdot l^{-1}$) and made up to 1 l with water. The buffer is freshly prepared before use.

Mianserin solution:

Mianserin.HCl (0,301 mg) is dissolved in 10 ml water (concentration 10^{-4} $mol \cdot l^{-1}$). An aliquot of 0,050 ml is used for the determination of non-specific binding (final concentration 10^{-5} $mol \cdot l^{-1}$ reaction mixture).

A suspension containing 3T3 cell homogenate:

NIH/3T3 cells are stably transfected with human $5HT_{2C}$ clone 9. The cells are grown in 3,6 l DMEM/HAM F12 (1 : 1) + 5 % (v/v) newborn-bovine serum (Hyclone) on Cultispher-G (5 $g \cdot l^{-1}$) microcarriers in a Celligen bioreactor. The cells are cultivated under stirring at 37 °C, pH 7 - 7,4. Fresh medium is added continuously by perfusion at a rate of 1,8 l DMEM/HAM per day and after two weeks a final cell density of approx 5,5 x 10^6 cells$\cdot ml^{-1}$ was obtained.

After termination of the stirring and consequent settlement of the microcarriers the supernatant is sucked up and the cells are removed from the microcarriers by incubation under stirring in 800 ml phosphate buffer solution (8 $g \cdot l^{-1}$ NaCl; 0,2 $g \cdot l^{-1}$ KCl; 1,15 $g \cdot l^{-1}$ Na_2HPO_4; 0,2 $g \cdot l^{-1}$ KH_2PO_4) containing EDTA (1 $mmol \cdot l^{-1}$). Following settlement of the carriers the supernatant, containing the cells, is collected. This removal step is repeated 4 times to give approx 1 x 10^{10} cells which are centrifuged at 30.000 $N \cdot kg^{-1}$ for 5 min.

The supernatant is removed and the cells are suspended in 250 ml Tris buffer (0,05 $mol \cdot l^{-1}$) using a Polytron homogenizer (15 s, max speed). The homogenate is incubated for 10 min at room temperature and then centrifuged at 400.000 $N \cdot kg^{-1}$ for 20 min. The pellets are resuspended in Tris-$MgCl_2$ buffer using the Potter-Elvehjem homogenizer to give a concentration of 2 x 10^7 cells$\cdot ml^{-1}$ per Eppendorf tube. The homogenate is frozen and stored at -70 °C. Before use the homogenate of 3 Eppendorf tubes (sufficient for one 96-wells micromedia rack or 96 reaction tubes) is allowed to thaw and resuspended in 45 ml Tris-$MgCl_2$ buffer using a Polytron homogenizer (15 s, max speed).

Procedure:

a. Estimation of total mesulergine binding:

0,050 ml Tris-$MgCl_2$ buffer, labelled mesulergine solution (0,050 ml) and 3T3 cell homogenate (0,40 ml) are successively pipetted in triplicate into wells of a micromedia rack or into glass test tubes. Immediately after the addition of the homogenate, the mixture is incubated by shaking for 60 min at room temperature. The incubation is terminated by filtration of the whole volume through the Whatman GF/B glass fibre, presoaked in Prosil 28 (1 % v/v) for 1 h, into either:

1. the Skatron 96-wells Harvester. Each residue is washed for 10 s with about 10 ml ice-cold Tris buffer. Each filter + residue is sealed with a Meltilex dry scintillation plate, using a heatsealer, and transferred to a LKB-Betaplate counter. The samples are counted once for 2 min.

or:

2. the Brandell 24-wells Harvester. Each residue is washed for 10 s with about 10 ml ice--cold Tris buffer (0,005 $mol \cdot l^{-1}$). The filters are transferred to scintillation vials containing 2,5 ml Ultima Gold MV scintillation fluid. Each sample is counted once for 3 min in a Packard-Tricarb liquid scintillation counter.

b. Estimation of non-specific mesulergine binding:
Mianserin solution (0,050 ml), labelled mesulergine solution (0,050 ml and 3T3 cell homogenate (0,40 ml) are successively pipetted in triplicate into wells of a micromedia rack or into glass test tubes. The procedure is further processed as described under a.

c. Estimation of mesulergine binding in the presence of test or reference compound:
Test or reference compound solution (0,050 ml), labelled mesulergine solution (0,050 ml) and 3T3 cell homogenate (0,40 ml) are pipetted in triplicate into wells of a micromedia rack or into glass test tubes. The procedure is further processed as described under a.

d. Estimation of total mesulergine radioactivity:
Labelled mesulergine solution (0,050 ml) is pipetted into a scintillation vial and 2,5 ml Ultima Gold MV scintillation fluid is added. The sample is counted once for 2,5 min using a liquid scintillation counter.
Ref. compound: Mianserin HCl: 10^{-8} $mol \cdot l^{-1}$ induces an inhibition of approx 70 %.

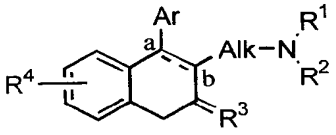
Compound concentrations

Test compounds are dissolved in the vehicle (Ultrapure water or HCl (0,1 $mol \cdot l^{-1}$) followed by neutralization to pH 7 - 8) and usually investigated in triplicate at 4 concentrations (10^{-5} ; 10^{-6}; 10^{-7} and 10^{-8} $mol \cdot l^{-1}$ reaction mixture) using the same batch of 3T3 cell homogenate.

Evaluation of responses:

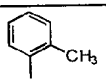
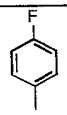
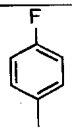
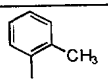
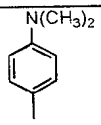
All responses are processed using a computer program. Counting figures can be expressed as counts per min (cpm) or can be corrected for quenching and converted as numbers of desintegrations per min (dpm). For each concentration of test compound the mean cpm- or dpm value is calculated. The mean percentage change of specific binding for each concentration, IC_{50}-values and affinity constants K_i for the binding of the test compound to the $5HT_{2C}$ receptor are calculated using methods well known in the art.

Results:



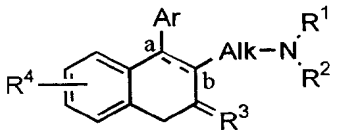
Com-pound (R^4 is H)	a·····b	Alk	R^1	R^2	R^3	Ar	pK_i for 5-HT_{2C}
1	—— (+)cis	-C-C-	CH_3	H	H		7.8
2	—— (±)cis	-C-C-	CH_3	CH_3	H		7.7
3	—— (+)cis	-C-C-	CH_3	CH_3	H		7.8
4	=	-C-C-	CH_3	CH_3	H		8.2
5	—— (±)cis	-C-C(CH_3)$_2$-	CH_3	CH_3	H		7.1

Table continued

Compound (R^4 is H)	a·····b	Alk	R^1	R^2	R^3	Ar	pK_i for 5-HT_{2C}
6	— (±)trans	-C-	CH_3	H	H		7.2
7	=	-C-C-C-	CH_3	H	H		7.4
8	=	-C-C-	CH_3	CH_3	CH_3		7.6
9	— (±)cis	-C-C-	CH_3	CH_3	H		7.6
10	— (±)cis	-C-C-	CH_3	CH_3	H		8.2
11	— (+)cis	-C-C-	CH_3	CH_3	H		8.6
12	=	-C-C-	CH_3	CH_3	H		8.3
13	=	-C-C-	CH_3	CH_3	H		8.3
14	=	-C-C-	CH_3	CH_3	H		7.8
15	=	-C-C-	CH_3	CH_3	H		7.7

Claims:

1. An aryl-hydronaphthalenalkanamine, having the structural formula,



wherein

R^1 and R^2 each independently are H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl, C_4-C_6-cycloalkenyl or C_1-C_6-alkoxy-C_1-C_6-alkyl;

R^3 is (H,H) or (H,CH_3);

R^4 is a hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfonyl, C_2-C_6 alkenyloxy, C_2-C_6-alkenylthio, C_2-C_6-alkenylsulfonyl, C_2-C_6-alkynyloxy, C_2-C_6-alkynylthio, C_2-C_6-alkynylsulfonyl, aminocarbonyl, cyano , halogen, trihalomethyl, aminosulfonyl, nitro and di(C_1-C_6)-alkylamino-group;

Ar is a phenyl, a naphtyl or a heteroaryl group, whereby phenyl- or pyridinyl-groups carry optionally one or more C_1-C_4-alkyl-, C_1-C_4-alkoxy-, C_1-C_4-alkylthio-, halo-, trihalomethyl-, cyano-, nitro- or dimethylamino-substituents;

Alk represents a C_2-C_6-branched, unbranched or cyclised saturated alkylene with a length of 2 - 3 carbons between the carbon ring and the amine function;

the a-b bond being a single or a double bond, to which side groups are in the trans or cis position;

and an addition salt or solvate thereof.

2. An aryl-hydronaphthalenalkanamine having the formula of claim 1 characterised in that

R^1 is hydrogen or methyl;

R^2 is methyl;

R^3 is (H,H);

R^4 is hydrogen;

Ar is phenyl, optionally with halo- or trihalomethyl-substituent in the 3 or 4 position of the phenyl group;

Alk is ethylene;

the a-b bond being a single bond, to which side groups are in cis position;
and an addition salt thereof.

3. An aryl-hydronaphthalenealkanamine having the formula of claim 1 characterised in that
R^1 is methyl;
R^2 is methyl;
R^3 is (H,H);
R^4 is hydrogen;
Ar is phenyl, optionally with chloro- or fluoro-substituent in the 3 or 4 position of the phenyl group;
Alk is ethylene;
the a-b bond being a single bond, to which side groups are in cis position;
and an addition salt thereof.

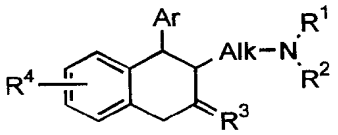
4. A pharmaceutical composition comprising a compound according to any one of the claims 1-3 in admixture with a pharmaceutically acceptable carrier.

5. The use of a compound according to any one of the claims 1-3 for the manufacture of a composition to effectuate partial or complete blockade of serotonergic 5-HT_{2C} receptors in an organism.

6. The use of a compound according to any one of the claims 1-3 for the preparation of a medicament for the treatment of psychiatric and neurological diseases.

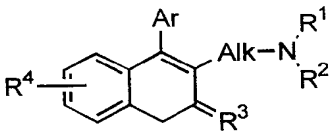
7. The use of a compound according to any one of the claims 1-3 for the preparation of a medicament for the treatment of anxiety disorders.

8. A process for the preparation of a compound of formula (II)



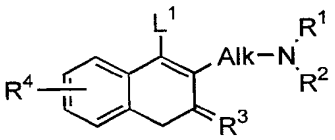
Formula (II)

wherein R^1, R^2, R^3, R^4, Alk and Ar are as defined in claim 1, provided that R^1 and R^2 are both different from hydrogen, characterised in that a compound of formula (III), wherein R^1, R^2, R^3, R^4 and Alk have the same meaning as in Formula (II), is hydrogenated with a reducing agent,



Formula (III)

and that a compound of formula (VII)



Formula (VII)

wherein R^1, R^2, R^3, R^4 and Alk have the same meaning as in Formula (II) and L^1 is a leaving group, is combined with an optionally substituted aryl- or heteroaryl-lithium, -magnesium, -zinc or -boron reagent in the presence of palladium salts or complexes.